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THE ROLE OF AGE ON DISTANT RECURRENCE AFTER BREAST CONSERVATIVE THERAPY *VS.* MODIFIED RADICAL MASTECTOMY AMONG IRANIAN PATIENTS WITH EARLY STAGE OF BREAST CANCER

F. SHAMSI[1], A. REZA BAGHESTANI[2], A. AKHAVAN[3], P. BASTANI[4]

[1]Department of Biostatistics and Epidemiology, Abortion Research Centre, Yazd Reproductive Science Institute, School of Public Health, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[2]Physiotherapy Research Centre, Department of Biostatistics, School of Allied Medical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[3]Department of Radiolooncology, School of Medicine, Cancer Prevention Center, Seyyed Al-Shohada Hospital, Isfahan University of Medical Sciences, Isfahan, Iran
[4]Department of Surgery, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

Abstract – *Objective:* *Breast conserving therapy is highly recommended for the surgical management of patients with early-stage of breast cancer. This study aimed to explore the effect of age on developing distant metastasis following breast conserving therapy or modified radical mastectomy.*

Patients and Methods: *To this aim, medical records of 468 women diagnosed with T1-2, N0-1, and M0 primary invasive breast cancer during 2005-2012 were selected. Patients were treated with either breast conserving therapy or modified radical mastectomy with post-surgical radiation. Kaplan-Meier method was used to estimate the breast cancer-free survival and distant metastatic-free survival rates. Distant metastasis and prognostic factors were modeled by Cox proportional hazards. The Bayesian approach was used to determine the po-tential threshold of patients' age at operation and the cure probabilities were estimated through two treat-ment types according to age change-point.*

Results: *There was no significant difference in Locoregional recurrence between two treatments type (p=0.83), although a significantly greater recurrence of distant metastasis was observed in the breast conserving therapy group (p<0.001). Considering metastatic-free survival, the age of 40 was estimated as the change-point of age at operation leading to a higher noticeable cure rate in the modified radical mastectomy group.*

Conclusions: *Older patients with early-stage of breast cancer treated with modified radical mastectomy had a significant decrease of distant metastasis compared with younger patients with a threshold of 40 for age at operation.*

KEYWORDS: *Early-stage, Breast cancer, Breast conserving therapy, Modified radical mastectomy, Age, Distant metastasis.*

INTRODUCTION

Breast conserving therapy (BCT) including lumpectomy following radiation therapy is known as an accepted alternative treatment to modified radical mastectomy (MRM) or mastectomy (MT) with or without postoperative radiation for early-stage of breast cancer. Although MRM as an invasive treatment includes complete removal of the breast, tumor, overlying skin, and axillary affected lymph nodes, some reported increasing MT or MRM rates among all age groups with early-stage of breast can-

Corresponding Author: Ahmad Reza Baghestani, PhD; e-mail: Baghestani@sbmu.ac.ir

cer[1-4]. The overall, recurrence-free, or disease-free survival after conservative therapy and MRM or MT for the early-stage of breast cancer patients have been investigated in different clinical and population-based studies[5-11]. Some studies indicated at-least equivalent overall survival (OS), distant metastasis-free survival (DMFS), breast cancer-specific survival (BCSS) and local/regional recurrence (LR/RR) for the patients treated with BCT, MRM or MT without considering postoperative radiation in T1-2N-N+M0[7,9,11-13]. Lumpectomy plus postsurgical radiation is proposed as the first course of treatment in some observational investigations[10,14-16]. These studies revealed noticeable higher OS, DMFS in the BCT group compared to MT. However, some breast cancer patients prefer receiving MRM than BCT in Asian countries[17]. Socioeconomic status is the predominant factor in choosing the more invasive surgery. Selecting an appropriate treatment is strongly related to typical prognostic factors such as tumor size, affected lymph nodes, hormone receptors status (immunohistochemical staining status including estrogen and progesterone receptor (ER/PR), and epidermal growth factor receptor-2 (Her2))[18]. Besides, locoregional recurrence of breast cancer, the occurrence of distant metastasis (DM), reconstruction techniques, and potential adverse effects of radiation therapy after surgery can influence the process of decision making[19,20].

In recent researches, unlike the results of a population-based study in American patients, age is considered as an influential factor for experiencing LR/RR or DM which may change the overall survival of breast cancer patients[21-25]. It was indicated in two Asian studies that breast cancer-specific survival and DMFS decreased in younger patients[23,24]. It was shown in one population-based study in Dutch patients diagnosed with I-II stages of breast cancer that the LR rate decreased in the BCT group for women younger than 40 years old[21]. Furthermore, the results of another study in Netherland revealed that overall survival decreased significantly with increasing age. However, no age-specific differences were observed in experiencing LR/RR and DM in breast cancer patients younger or older than 75 years old. Accordingly, it was suggested to conduct age-specific breast cancer studies to find the actual impact of age in a heterogeneous group of patients[22].

Breast cancer management for young patients with early-stage of cancer changed considerably into a multidisciplinary approach including less radical surgery following radiation therapy, chemotherapy, or hormonal therapy. Considering the situation of patients involved in different types of surgery, it has been reported that younger patients are more susceptible to aggressive stages of breast cancer. Consequently, controlling the LR/RR and DM recurrences after completing treatment are considered important. In a systematic meta-analysis including five population-based studies and one clinical trial comparing OS based on treatment types (BCT or MT) in young patients (≤40 years) with early-stage of breast cancer, the equivalent long-term results were reported[26]. As mentioned, on Korean patients aged ≤ 30 with early-stage of cancer, no significant difference was observed in 5- and 10-year overall survival between BCT and MT groups. However, there was a noticeable lower LR rate in patients treated with MT in long-term follow-up[23]. Considering various age groups in different researches may lead to ambiguous inferences about the importance of age on cancer recurrences. Frequently, a proportion of treated cancer patients may not experience the event of interest such as LR/RR, DM up to the end of long-term follow-up are regarded as cured or long-term survivors. Generally, the stable plateau at the tail of Kaplan-Meier curves is considered as empirical evidence for the presence of a cured fraction. Cure models that handle the heterogeneity in treated patients are preferred in survival analysis for evaluating the actual prognostic effect of predictors[27-30]. This study aims to investigate the influence of age as an important factor which may cause variation in oncological outcome in different surgical treatments of T1-2N0-1M0 breast cancer patients. To this aim, the mixture cure model was considered for modeling survival data and the Bayesian approach was applied to detect the threshold of age at operation in the early stage of breast cancer patients[31].

PATIENTS AND METHODS

Participants

All data were extracted from a historical-cohort study database conducted at a university hospital in Iran during 2005-2012 [32]. Participants were female admitted to Shahid Sadoughi Hospital in Yazd who had a primary ductal or lobular carcinoma without any previous occurrence of cancer and were a candidate for breast-conserving surgery with radiotherapy (BCT) or MRM. Patients were admitted to Shahid Ramadanzadeh Radiotherapy Center for post-surgical radiation. The patients with no histological information, previous diagnosis of non-invasive breast cancer within five last years, any symptom of concurrent malignancy or metastatic tumor, and those undergoing chemotherapy or radiotherapy prior to surgery were excluded from the study. The study was limited to those patients with early stage of breast cancer (T1-2N0-1M0), who was divided as stage I

and II according to the tumor size, lymph nodes and metastases classification according to 7th edition of the American Joint Committee on Cancer (AJCC) system. The study included 468 patients who underwent breast conserving surgery following radiation therapy or MRM with post-surgical radiation. Those patients who were treated with MRM without radiation therapy were excluded as the patients commonly receive postsurgical radiation after MRM surgery. Demographic and clinicopathologic factors including age of patients at operation, grade, tumor size, lymph nodes status, ER, PR and Her2 status, histology, presence of lymphovascular invasion, adjuvant treatment such as chemotherapy or hormone therapy, and type of surgery were measured for the primary tumor. Continuing tamoxifen as an adjuvant treatment to 10 years was recommended for patients[33]. Besides, the molecular subtypes of breast cancer were also defined as Luminal A (ER+/PR+/HER2-/low Ki-67); Luminal B (ER+/PR+/HER2-/ high Ki-67); HER2-overexpression (ER-/PR-/HER2+) and triple-negative (ER-/PR-/HER2-) according to the classification of immunohistochemistry (IHC) markers[34, 35]. The basal-like subtype was not identified because the basal marker (CK5/6) was not recorded for patients[36,37]. The information was extracted from pathology reports and medical files during the follow-up. All patients provided written informed consent. The approval of this study was obtained from the Medical Ethical Committee of the Shahid Beheshti University of Medical Sciences (IR.SBMU.RETECH.REC.1397.822), and the Ethics Committee of the Shahid Sadoughi University of Medical Sciences gave confirmation.

Follow-up and endpoints

Postoperative follow-up was performed until March 20, 2017. Local recurrence, DM-free survival situations, and survival time were followed simultaneously. The primary and secondary endpoints of this study were distant metastasis and death during the follow-up, respectively. Time-to-event was identified as the interval between the date of surgery and DM occurrence or death from breast cancer, separately. In the absence of events of interest at the last follow-up, the subjects were censored.

Statistical analysis

First, the χ^2 test was used to compare the demographic and clinicopathologic factors between the two groups. Survival rates were estimated with the Kaplan-Meier method, and the effect of each variable on DM-free survival and OS curves were determined using the log-rank test. Hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated for both DM-free survival and OS for all factors using the unadjusted and adjusted Cox proportional hazard model. Also, the potential threshold of the effective quantitative covariates on DM-free survival was determined using the Bayesian approach by considering the cure proportion of patients using R software (https://cran.r-project.org/)[31]. p-value <0.05 was considered as statistically significant.

RESULTS

In general, 468 patients ranged 22-81 years with a median age of 47 years (Interquartile range (40-54 years)) were included in this study, among which 261 patients (55.8%) underwent BCT and 207 patients (44.2%) underwent MRM with post-surgical radiation. The median follow-up time for DM and death was 4.7 and 5 years, respectively. The tumor baseline characteristics of patients according to received treatments are shown in Table 1. As shown, among BCT group 58 (22%) distant metastasis and 13 (5%) LR/RR occurred. Results indicated patients in the BCT group had higher mean age at operation, larger tumor size, more axillary affected lymph nodes status, and more lymphovascular invasion (LVI) compared to those who underwent MRM with post-surgical radiation. However, the patients in the MRM group were more likely to have a higher value of the ki-67 index. There was no significant difference between the patients in both treatment groups regarding tumor type, tumor grading, ER-/PR- status, Her2/neu-positive carcinoma status, adjuvant chemotherapy, and molecular subtype classification.

After completing follow-up time, 87 patients died, among whom 18 (9%) and 69 (26%) died from MRM and BCT group, respectively, while 381 patients were alive. Kaplan-Meier estimates indicated a significant improvement in OS and DMFS curves for MRM over the BCT group, and Log-rank tests revealed a statistically significant difference between the survival curves for both results, respectively (p-value<0.001) (Figures 1 (A) and (B)).

Using MRM with postsurgical radiation group as reference, univariable Cox model analysis indicated that patients assigned to the BCT group (HR=3.09, 95% CI: 1.75-5.46) had a higher risk of experiencing DM. As indicated in Table 2, involving axillary lymph nodes increased the risk

TABLE 1. Clinical Characteristics of early stage of breast cancer Patients by surgery type.

Characteristics	*BCT n=261 (56%)*	*MRM with post-surgical radiation n=207 (44%)*	*p-value*
	(%)	*N (%)*	
Vital status			<0.001
Dead	69 (26)	18 (9)	
Alive	192 (74)	189 (91)	
Distant metastasis			<0.001
Yes	58 (22)	15 (7)	
No	203 (78)	192 (93)	
Locoregional recurrence			0.83
Yes	13 (5)	9 (4)	
No	248 (95)	198 (96)	
Age at surgery time (years), mean (SD)	48.92±10.96	45.83±10.51	0.002
Tumor size			<0.001
T1 <2	36 (14.9)	65 (32.2)	
T2 2-5	190 (78.5)	126 (62.4)	
T3 >5	16 (6.6)	11 (5.4)	
Tumor type			0.35
Ducal	197 (75.5)	155 (74.9)	
Lobular	24 (9.2)	13 (6.3)	
Other	40 (18.8)	39 (15.3)	
Affected Lymph nodes			<0.001
N0	51 (19.5)	111 (53.6)	
N1 1-3	210 (80.5)	96 (46.4)	
Tumor Grade			0.09
I	27 (10.3)	14 (6.8)	
II	104 (39.8)	93 (44.9)	
III/IV	53 (20.3)	54 (26.1)	
Unknown	77 (29.5)	46 (22.2)	
Lymphovascular invasion			<0.001
Yes	59 (22.6)	27 (13)	
No	112 (49.2)	132 (63.8)	
Unknown	90 (34.5)	48 (23.2)	
Estrogen/progesterone receptors (ERPR)			0.16
ER+PR+	103 (39.5)	98 (47.3)	
ER-PR-	62 (23.8)	37 (17.9)	
unknown	96 (36.8)	72 (34.8)	
Her2 status			0.22
Negative	54 (20.7)	52 (25.1)	
Positive	122 (46.7)	102 (49.3)	
unknown	85 (32.6)	53 (25.6)	
Ki67			0.002
≤15	41 (15.7)	56 (27.1)	
>15	41 (15.7)	40 (19.3)	
unknown	179 (68.6)	111 (53.6)	
Adjuvant chemotherapy			0.42
Yes	238 (91.2)	192 (93)	
No	23 (8.8)	14 (6.6)	
Unknown	0	1 (0.4)	
Molecular subtype classification			0.8
Luminal A	48 (34.5)		41 (30.6)
Luminal B	83 (59.7)		84 (62.7)
Triple negative	5 (3.6)		7 (5.2)
HER2 positive	3 (2.2)		2 (1.5)

of DM (p-value=0.001). Patients were grouped in two according to age at the operation to determine its effect more clearly. In this regard, patients who were ≥ 40 years old were more likely to develop DM compared to those aged lower than 40 years old (Table 2). Other prognostic factors had a similar effect on experiencing DM in both treatment groups.

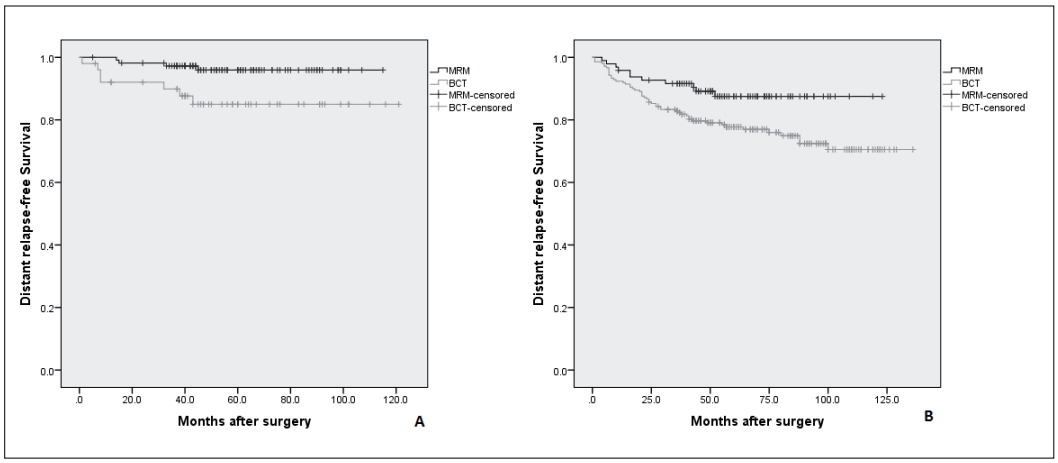

Fig. 1. ***A***, Overall survival and (***B***) Distant relapse-free survival according to types of treatment in breast cancer patients.

TABLE 2. Univariable analysis of DM-free survival for early-stage of breast cancer patients.

Characteristics	*Univariable analysis Time to distant metastasis*	
	HR (95% CI)	*p-value*
Treatment		
MRM with postsurgical radiation	Ref	
BCT	3.09 (1.75-5.46)	<0.001
Age at surgery time (years)		
≤40	Ref	
>40	0.64 (0.4-1.05)	0.075
Affected lymph nodes		
N0	Ref	
N1	2.91 (1.53-5.54)	0.001
Tumor size		
T1	Ref	
T2	1.56 (0.81-2.98)	0.18
T3	0.67 (0.15-3.03)	0.6
Grade		
I	Ref	
II	1.78 (0.63-5.03)	0.27
III/IV	2.05 (0.69-6.03)	0.19
Tumor Type		
Ductal	Ref	
Lobular	1.03 (0.47-2.26)	0.93
Other	0.43 (0.18-0.98)	0.046
LVI		
Yes	Ref	
No	0.83 (0.44-1.57)	0.57
Estrogen/progesterone receptors (ERPR)		
ER+PR+	Ref	
ER-PR-	1.61 (0.9-2.88)	0.1
Her2 status		
Positive	Ref	
Negative	1.48 (0.81-2.7)	0.2
Ki67		
≤15	Ref	0.76
>15	1.52 (0.46-2.86)	
Adjuvant chemotherapy		
Yes	Ref	
No	1.4 (0.67-2.93)	0.36
Molecular subtype classification		
Luminal A	Ref	
Luminal B	0.97 (0.36-1.37)	0.3
HER2 positive	2.59 (0.59-11.35)	0.2
Triple negative	3.41 (1.23-9.45)	0.02

TABLE 3. Multivariable Analysis of DM-free survival for early-stage of breast cancer patients.

Characteristics	*Time to metastasis HR* (95% CI)*	*p-value*
Model 1		
Treatment		
MRM with postsurgical radiation	Ref	
BCT	2.67 (1.44-4.96)	0.002
Age at surgery time (years)		
≤40	Ref	
>40	0.6 (0.36-1.01)	0.046
Affected lymph nodes		
N0	Ref	
N1	2.17 (1.07-4.39)	0.03

Regarding the multivariable Cox regression analysis, the backward method was recognized as the most appropriate approach to assess the effect of each adjusted variable and presenting the most fitted model. Based on the backward method, the established prognostic factors such as tumor size, nodal status, tumor grade, ER/PR status, Her2 status, molecular subtype classification, and adjuvant chemotherapy were considered in the model and the concluding model was achieved after removing the non-significant variables (Table 3). Compared to the patients who received MRM followed by radiation, those treated with BCT had a higher risk of occurring distant metastasis (HR=2.67, 95% CI 1.44-4.96) after adjusting to age and lymph node status. Furthermore, the age at operation and nodal status were considered as influential parameters in experiencing DM (Table 3).

The appropriateness of conducting a cure rate model was indicated in Figures 1 (A) and (B), respectively, considering a stable region after 50 and 100 months for MRM and BCT groups. The present study aimed to fit the correct model to estimate the actual effect of significant covariates on time to DM occurrence utilizing an appropriate approach for detecting the thresholds of effective continuous variables. As shown in Figure 1 (B), the patients in the MRM group after 50 months cured for developing DM at the end of follow-up time and they may not die after 60 months. Figures 2 (A) and (B), Figures 3 (A) and (B) highlighted the difference between the cure rates in both treatment groups by considering the patient's age categories and nodal status, respectively. A significant difference between cure rates demonstrated that the classification of these two variables could help choose the appropriate treatment for patients with stage I and II of breast cancer. Previous studies suggested different methods to estimate a change-point of a quantitative variable[38,39]. The Bayesian approach was selected for detecting the threshold of patients' age at operation through different latent distributions[31]. As shown in Table 4, different Bayesian models were speci-

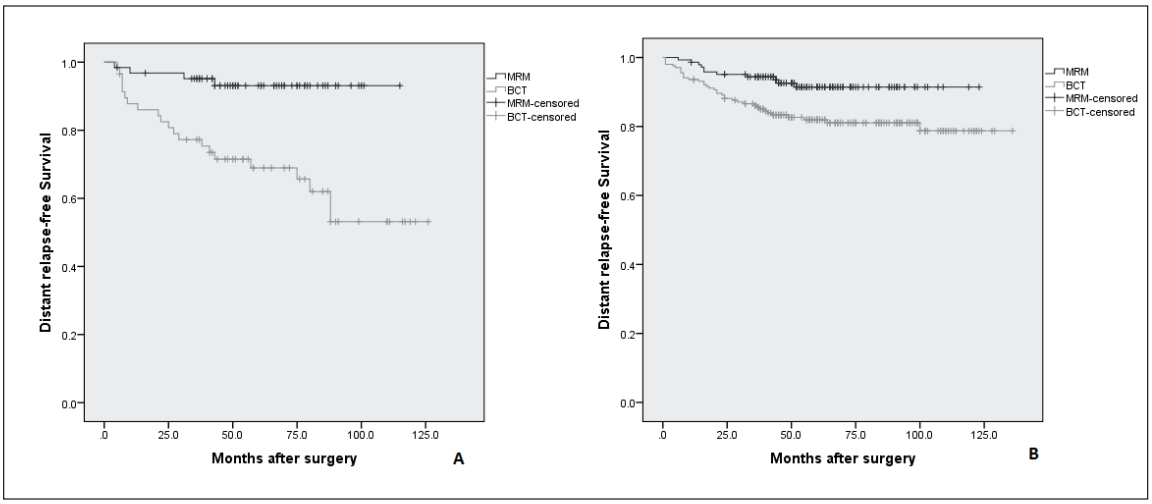

Fig. 2. ***A***, Distant metastasis-free survival according to types of treatment in early-stage breast cancer patients aged ≤40 and (***B***) in early-stage breast cancer patients aged >40.

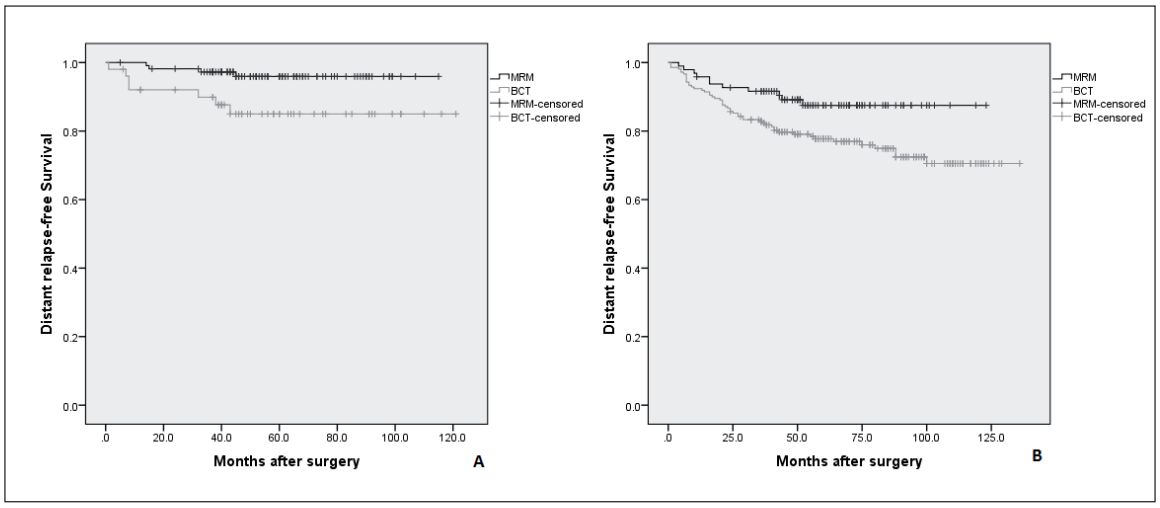

Fig. 3. ***A***, Distant metastasis-free survival according to types of treatment in early-stage breast cancer patients with negative nodule status and (***B***) with positive nodule status.

fied and the threshold of patients' age at operation was estimated. Considering DIC values, model 3 had the best performance and the threshold of age was estimated 40 years old as expected. Based on model 3 in Table 4, the odds of cured patients in MRM with postsurgical radiation groups were 11 times higher than the BCT group for women at or younger than 40 years old compared to older patients. Regarding the significant difference in cure rates between two types of surgery, the Bayesian approach provided some shreds of evidence that the age of patients at operation could modify the effect of treatment types, which was observed in Kaplan-Meier estimations (Figures 3 (A) and (B)).

DISCUSSION

Surgical management for the early stage of breast cancer has been gradually developed from radical surgery to sophisticated surgical procedures. this sequence of instructions is determined for oncological safety and improvement of life quality. The outcome of breast cancer patients is affected by

TABLE 4. Multivariable Analysis of DM-free survival for early-stage of breast cancer patients.

Characteristics	β	*SE*	*Exp (β)*	*95% HPD Interval*
Model 1: Mixture cure model with threshold with exponential latency				
Age at surgery time (years)≤ 35				
MRM with postsurgical radiation BCT	0.4 ref	0.32	1.49	(-0.18, 0.96)
Age at surgery time (years)> 35				
MRM with postsurgical radiation BCT	1.06 ref	0.35	2.88	(0.37, 1.62)
Model 2: Mixture cure model with threshold with log-logistic latency				
Age at surgery time (years)≤ 34				
MRM with postsurgical radiation BCT	0.87 ref	0.41	2.38	(0.05, 1.53)
Age at surgery time (years)> 34				
MRM with postsurgical radiation BCT	1.41 ref	0.29	4.09	(0.91, 1.94)
Model 3: Mixture cure model with threshold with Weibull latency				
Age at surgery time (years)≤ 40				
MRM with postsurgical radiation BCT	2.4 ref	0.62	11.02	(1.14, 3.53)
Age at surgery time (years)> 40				
MRM with postsurgical radiation BCT	1.53 ref	0.83	4.62	(0.32, 3.29)

SE, standard error of mean; HPD, highest posterior density.

the complex interactions between tumor biology, patients' features, and received treatment. In the early stage of breast cancer, the tumor features are almost similar, and host conditions can influence the treatment choice and outcome[40]. Although some investigations indicated that younger and older patients may benefit from BCT or MRM equally, age should be considered as a time-dependent covariate and effective factor in process of treatment decision-making that can enhance the surgeon's knowledge to predict the treatment outcome[13,15]. There are some reasons persuaded researchers to focus on long-term outcome of each treatment in various age groups among breast cancer patients such as high incidence of breast cancer in young women, increasing rate of MT or MRM rather than BCT in some nations[2,4,41], fear of cancer recurrence after treatment, postsurgical treatment such as radiotherapy or chemotherapy, established oncology safety of BCT and improved quality of life in younger patients with early-stage of breast cancer[23,42], reported at-least similar OS and DM-free survival after BCT or MT among young and old aged of patients with early-stage of breast cancer[6,7,16,25]. Besides, the shape of the relationship between patients' age and cancer relapse or death, especially at 40-45 years of age, may represent different cancer progression trends according to age[24, 43].

The present study focused on the change-point estimation of the patients' age at operation concerning treatment for early-stage of breast cancer. Most of the previous studies evaluated the effect of age in the dichotomous method by using various definitions of youth[13,22-24]. In this observational study, the effect of BCT and MRM on a cured fraction of patients, considering DM occurrence, were compared based on the estimated threshold of patients' age. Results indicated treatment types and nodule status were significantly important, and the age at operation had a borderline effect on developing DM after adjusting to other clinicopathological and histopathological features (Table 2). In line with the results of the previous studies, the cured proportion of treated early breast cancer patients increased for patients older than 40 years old, as shown in Figures 2 (A) and (B). The Bayesian method using a mixture cure rate model with Weibull distribution as the latency part, determined the threshold of patients' age at operation at about 40 years old (Model 3 in Table 3)[31]. To summarize the results, a significant difference was observed between the probabilities of not experiencing DM in each surgery type for patients younger than 40 years old compared to older ones (Table 3).

The main finding of this study that OS and DM-free survival was longer for all patients treated with MRM with postsurgical radiation, especially in patients aged lower than 40 years old, confirms the results of previous meta-analysis study showing better OS for patients treated with MT compared to breast conserving surgery with whole breast radiotherapy group in early breast cancer patients aged 40 years or younger[26]. Furthermore, the detected threshold was exactly similar to what was reported from the Asian breast cancer study and the same rates were calculated for OS[24]. However, other studies had shown no association between age and overall survival in different surgery types[13,23]. An explanation for this discrepancy could be attributed to more regularly receiving postsurgical radiation in the MRM group that caused a significant difference in cure probabilities between two treatments in younger patients. Some studies reported an increased risk of local recurrence in the BCT group for younger patients, while no difference was observed in OS rate[15,23,24]. Based on the results of the present study, no significant difference was observed in locoregional recurrence between two surgery types in both age groups of patients, despite some differences in DM recurrence. In the BCT group, the risk of experiencing DM was 2 times higher for patients younger than 40 years old.

The use of Bayesian approach to detect the threshold of a challenging covariate in DM-free survival is considered as the main benefit in the present study. Moreover, examining different distributions for identifying the correct threshold of patient's age at operation can be regarded as its flexibility. Based on the results of previous research, postsurgical radiation is an effective factor for better OS in BCT group[44]. All patients in the present study received postsurgical radiation after each surgery for completing their treatment process that helped to obtain a realistic view of treatment effects afforded by the two surgical types.

The selection bias and recording information errors before designing the study were considered as some of the limitations in the present study, which caused removing some cases. Furthermore, small DM occurrences in patients under the age of 40 could be regarded as a reason for increasing comorbidities. Long-term follow-up, at least 10 years or higher can eliminate the limitation demonstrating the treatment effect more noticeable.

CONCLUSIONS

In conclusion, this study aimed to detect the correct threshold of patients' age at operation for demonstrating the influence of each surgery type after a 5-year follow-up. Based on the results,

younger patients with early-stage of breast cancer treated with BCT were inclined to a higher risk of experiencing DM compared to the MRM group. A definite threshold of age at operation was first determined to calculate the cure probabilities through two types of surgery. Patients' age can be regarded as an effective factor in the decision-making process for early stage patients that may increase the number of long-term survivors while an appropriate treatment should be selected with comprehensive consideration.

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Conflict of interest:
There are no conflicts of interest.

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